PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 502-189PCT	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/IB2005/002480	International filing date *(day/month/year)* 26 January 2005 (26.01.2005)	Priority date *(day/month/year)* 26 January 2004 (26.01.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant DEBIOVISION INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

   - ☒ Box No. I — Basis of the report
   - ☐ Box No. II — Priority
   - ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV — Lack of unity of invention
   - ☒ Box No. V — Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI — Certain documents cited
   - ☐ Box No. VII — Certain defects in the international application
   - ☐ Box No. VIII — Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 27 July 2006 (27.07.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Cecile Chatel e-mail: pt13@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

8/12
PT13

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No. PCT/IB2005/002480	International filing date *(day/month/year)* 26.01.2005	Priority date *(day/month/year)* 26.01.2004

International Patent Classification (IPC) or both national classification and IPC
C07K14/705, C07K16/30

Applicant
ONCOMAB GMBH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Irion, A

Telephone No. +49 89 2399-8174

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2005/002480

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 20-36,48-50,55

because:

☒ the said international application, or the said claims Nos. 20-36,48-50,55 (IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2005/002480

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	3-9, 11-14, 20-23, 26-34, 38, 48, 49, 52, and 54
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-57
Industrial applicability (IA)	Yes:	Claims	1-19,37-47,51-54
	No:	Claims	

2. Citations and explanations

see separate sheet

Item III

III.1 With respect to claims 20-36, 48-50, and 55

Claims 20-36, 48-50, and 55 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(I) PCT).

Item V

V.1 Reference is made to following documents

D1: WO03011907 (H.K. MÜLLER-HERMELINK ET AL.) 13 February 2003 (2003-02-13)

D2: VOLLMERS ET AL.: 'Human monoclonal antibodies from stomach carcinoma pateints react with Helicobacter pylori and stimulate stomach cancer cells in vitro', CANCER, 1994, vol. 74, pages 1525-1532

D3: F. HENSEL ET AL. : 'Mitogenic autoantibodies in Helicobacter pylori-associated stomach cancerogenesis', INTERNATIONAL JOURNAL OF CANCER, 12 April 1999 (1999-04-12) vol. 81, pages 229-235

D4: S. BRÄNDLEIN ET AL.: 'Cysteine-rich fibroblast growth factor receptor 1, a new marker for precancerous epithelial lesions defined by the human monoclonal antibody PAM-1', CANCER RESEARCH, 01 May 2003 (2003-05-01), vol. 63, pages 2052-2061

V.2 Novelty (Article 33(2) PCT)

V.2.1 With respect to claims 3-9, 11-14, 20-23, 26-34, 38, 48, 49, 52, and 54

Document D1 describes the sequences of the CFR-1 isoform and of the murine antibody designated 58/47-69 referred to as SEQ ID NO. 1-6 which are identical with the sequences of the present application referred to as SEQ ID NO. 1-6. D1 further identifies the binding region as a glycostructure and states that the CFR-1 isoform disclosed is tumor specific (p. 5 l. 4-15, p. 7 l. 18-20, p. 7 l. 31 - p. 8 l. 18). A screening method for identifying CFR-1 isoform specific binding agents is described (p. 5 l. 15-21, p. 10 l. 24-

32). Said agents identified may be used for diagnostic and therapeutic purposes (p. 4 l. 15-24). CFR-1 isoform is used for the vaccination/treatment against tumors and pre-cancerous cells (p. 8 l. 29 - p. 10 l. 9). Humanized murine antibodies are described which can be used for therapy (p. 11 l. 29-31). Furthermore, antibody fragments such as Fab, F(ab)2, Fab' and scFv are described (p. 11 l. 6-10), which do not comprise the full-length sequence of the antibody. The production of the human monoclonal IgM autoantibody designated 103/51 is described (p. 13 l. 1-5) (see also D2 to which D1 refers). However, the human antibody 103/51 is neither described by its sequence nor is deposited according to the Budapest Treaty. The cDNA of CFR-1 isoform has been cloned (p. 22 l. 25). Therefore, a vector and a cell comprising the nucleic acid sequence of SEQ ID NO. 5 is implicitly described. Moreover, the CFR-1 isoform is isolated form the adenocarcinoma cell line 23132 (p. 12 l. 25-27, claim 13).

D1-D4 are not considered enabling concerning the disclosure of said human antibody 103/51 although D3 discloses the amino acids 1-82 of said antibody.

Therefore, the subject-matter of claims 3-9, 11-14, 20-23, 26-34, 38, 48, 49, 52, and 54 is not considered novel in the sense of Article 33(2) PCT.

V.2.2 With respect to claims 1, 2, 10, 15-19, 24, 25, 35-37, 39-47, 50, 51, 53, and 55-57

The subject-matter of claims 1, 2, 10, 15-19, 24, 25, 35-37, 39-47, 50, 51, 53, and 55-57 is considered novel in the sense of Article 33(2) PCT.

V.3 Inventive step (Article 33(3) PCT)

V.3.1 With respect to claims 39-41, 43-47, 50, 53, 55-57

The subject-matter of claims 39-41, 43-47, 50, 53, 55-57 differs from the closest prior art document D1 in that the polypeptide derived from CFR-1 isoform does not comprise the full-length of SEQ ID NO.6, thus, differs from CFR-1 isoform disclosed in D1 by at least one amino acid. It is not apparent which technical problem might be solved by such a fragment of the protein referred to as SEQ ID NO. 6. Moreover, no single fragment falling under this definition is shown in the present application. Therefore, the subject-matter of claims 39-41, 43-47, 50, 53, 55-57 is not considered inventive in the sense of Article 33(3) PCT.

V.3.2 With respect to claims 15, 24, 25, 35, 36, and 51

The subject-matter of claims 51 differs from the closest prior art document D1 in that a method of protein purification using a vector encoding the CFR-1 isoform is used instead of isolating the protein directly from the cells in which the protein is naturally expressed. It falls under the daily routine practice of the skilled person to produce a known protein in a recombinant expression system by attaching a cleavable protein purification tag as it is described in claims 24, 25, 35, and 36. Therefore, the subject-matter of claims 15, 24, 25, 35, 36, and 51 is not considered inventive in the sense of Article 33(3) PCT.

V.3.3 With respect to claims 1, 2, 10, 16-19, and 37

The subject-matter of claims 1, 2, 10, 16-19, and 37 differs from the closest prior art document D1 in that the CDRs derived from the sequence of the human monoclonal IgM autoantibody designated 103/51 are disclosed. The technical problem to be solved may be regarded as providing an alternative antibody binding the CFR-1 isoform disclosed in D1 instead of the CDRs derived from the antibody designated 58/47-69. The production of an antibody against a known antigen falls under the daily routine practice of the skilled person. Therefore, the subject-matter of claims 1, 2, 10, 18, 19, and 37 is not considered inventive in the sense of Article 33(3) PCT.

V.3.4 With respect to claim 42

The subject-matter of claim 42 differs from the closest prior art document D1 in that the CFR-1 protein is at least 95% pure. The high purity of a protein is a natural need for many applications of said protein. Therefore, the skilled person being aware of methods for the effective purification of a recombinantly produced protein would use said methods thereby arriving at the subject-matter of claim 42. Therefore, said claims is not considered inventive in the sense of Article 33(3) PCT.

V.3.5 With respect to claims 16 and 17

The subject-matter of claims 16 and 17 does not confer an inventive step on the polypeptides of claim 1 and 3. Therefore, the subject-matter of said claims is not considered inventive in the sense of Article 33(3) PCT.

V.4 Industrial applicability (Article 33(4) PCT)

V.4.1 With respect to claims 1-19, 37-47, and 51-54

The subject-matter of claims 1-19, 37-47, and 51-54 appears to be susceptible of industrial application.

V.4.2 With respect to claims 20-36, 48-50, and 55

The subject-matter of claims 20-36, 48-50, and 55 is considered to be a method of diagnosis or a method of treatment by therapy of the human or animal body.

For the assessment of the present claims 20-36, 48-50, and 55 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.5 Further remarks

V.5.1 With respect to claims 28, 32, and 43

The term "58/47-69" appears to be an internal designation for the murine antibody defined by the sequences referred to as SEQ ID NO. 1-4. Such an internal desigantion cannot be used to defined the subject-matter of a claim. Therefore, claims 28, 32, and 43 do not meet the requirements of Article 6 PCT.

V.5.2 With respect to claim 51

The term "substantially" used in claim 51 is unclear. Therefore, the subject-matter of claim 51 does not meet the requiremtns of Article 6 PCT.

V.5.3 With respect to claim 56

The subject-matter of claim 56 does not appear to be part of the method claimed in claim 55. However, claim 56 refers to claim 55. Furthermore, the polypeptide purified from the cell line indicated appears to be the full-length protein, a fact which contradicts to the subject-matter of claim 39.

V.5.4 With respect to claims 1 and 2

The sequences referred to SEQ ID NO. 26 and SEQ ID NO. 27 disclosed in the Sequence listing are DNA sequences. However, the subject-matter of claim 1 and 2 refers to the amino acids of said sequences. Therefore, claims 1 and 2 and all claims being dependent on said claims do not meet the requirements of Article 6 PCT. (see also the description referring to SEQ ID NO. 26-29 (e.g. p. 3 l. 18-21).

V.5.5 With respect to claims 10, 13, 18 and 19

The sequences referred to SEQ ID NO. 28 and SEQ ID NO. 29 disclosed in the Sequence listing are protein sequences. However, the subject-matter of claims 10, 13, 18, and 19 refers to nucleic acid sequences. Therefore, claims 10, 13, 18, and 19 and all claims being dependent on said claims do not meet the requirements of Article 6 PCT.

V.5.6 With respect to claims 28 and 32

The subject-matter of claim 28 discloses the murine antibody 58/47-69 which comprises the whole sequence of said antibody. Claim 28 is dependent on claim 20, which itself is dependent on claim 3, in which the polypeptide is defined by not comprising the full-length of SEQ ID NO. 2. However, said antibody comprises the full-length of SEQ ID NO. 2. Therefore, claim 28 does not meet the requirements of Article 6 PCT. Same applies to claim 32.